Bevacizumab as a last-line treatment for glioblastoma following failure of radiotherapy, temozolomide and lomustine

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Abstract. In previous trials, bevacizumab failed to prolong the overall survival time in newly diagnosed glioblastoma and at the first recurrence. Randomized clinical trials at the second or further recurrence following the failure of radiotherapy, temozolomide and lomustine, and retrospective analyses focusing on this specific cohort, are not yet available. A total of 62 patients with glioblastoma who received bevacizumab after the failure of standard care, including radiotherapy, temozolomide and lomustine, were retrospectively identified. Patient characteristics, previous treatment details, concomitant therapy, response based on the Response Assessment in Neuro-Oncology criteria, and progression-free survival (PFS) and overall survival (OS) times and rates were evaluated. Furthermore, the PFS and OS times and rates were analyzed for responders and non-responders. Of the patients, 54.8% (n=34) responded to treatment [complete response (CR) 3.2%, n=2; partial response (PR) 51.6%, n=32]. The median PFS time was 3.5 months and the median OS time was 7.5 months. The PFS rate at 6 months was 21.5% and the OS rate at 12 months was 11.5%. Responders (CR or PR) experienced a superior median PFS time compared with non-responders (i.e. stable or progressive disease; 5.4 vs. 1.9 months; P<0.0001) and a superior PFS rate at 6 months (34.9 vs. 7.1%; P<0.0001). The median OS time (8.6 vs. 6.4 months; P<0.0001) and OS rate at 12 months (21.3 vs. 0%; P<0.0001) were also superior in patients who exhibited a response to bevacizumab treatment. In conclusion, the objective response rate and the PFS and OS times and rates indicate that bevacizumab has activity in patients with glioblastoma following the failure of radiotherapy, temozolomide, and lomustine. A randomized trial comparing bevacizumab with best supportive care in these patients is advised.

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Introduction

The prognosis of patients with glioblastoma is poor (1-3). Gross total resection, radiotherapy and more recently, alternating electric fields, improve the outcome (4-9). Chemotherapy with temozolomide improves overall survival (OS) time predominantly in patients with glioblastoma that harbor a methylated O-6-methylguanine-DNA methyltransferase (MGMT) promoter (10,11). Even in these patients, tumor progression is inevitable; at first progression, median progression-free survival (PFS) and median overall survival (OS) times typically reach 2-3 and 8-9 months, respectively (12). At progression, gross total resection can be achieved again in certain patients (13). Re-irradiation is also applied when technically possible (14). Temozolomide rechallenge and lomustine chemotherapy are frequently used to treat recurrent glioblastoma (12,15). Nonetheless, as demonstrated by low PFS and OS times, the efficacy of all approaches at recurrence is limited (12).

The anti-vascular endothelial growth factor-A antibody bevacizumab was approved for the treatment of patients with recurrent glioblastoma in a number of countries, including the United States (16). European authorities refused approval in the same year on the grounds of insufficient evidence for improved OS time (17). In 2014, the results of two randomized phase III trials on the use of bevacizumab with first-line treatment were published; these trials failed to show increased OS times when standard therapy was combined with bevacizumab (18,19). In recurrent glioblastoma, a randomized phase II trial indicated that bevacizumab combined with lomustine improves survival rate compared with lomustine alone (20). Therefore, a phase III

European Organization for Research and Treatment of Cancer trial (designated BELOREC) (21) was conducted to compare lomustine monotherapy with lomustine plus bevacizumab in patients with glioblastoma at first recurrence. The results were presented at the 2015 Society for Neuro-oncology annual meeting. As in the first-line trials, bevacizumab prolonged PFS time; however, OS time was not improved (21).

Besides being approved in a number of countries, bevacizumab may be reimbursed by health insurance companies in certain countries that lack approval (17). Procedures for reimbursement are heterogeneous in the EU. Whereas certain countries, including the Netherlands, refuse reimbursement in general, others, including France, have a more generous approach to access to bevacizumab for patients with glioblastoma. In Germany, reimbursement must be applied for; such applications are only promising if all treatment options (e.g. surgery and radiotherapy) and approved drugs (e.g. temozolomide and lomustine) have already been used for the specific patient. Due to the aforementioned negative study results, the reimbursement chance is likely to decrease in the future. Due to the reimbursement issue, although bevacizumab failed to prolong OS as a first-line treatment and at first recurrence after failure of radiotherapy and chemotherapy with temozolomide, crossover was a critical issue in the previously described trials (18-21). A relevant number of patients had been treated with bevacizumab in the control treatment arm.

Despite these negative trials, bevacizumab is widely used for the treatment of patients with recurrent glioblastoma. Randomized clinical trials comparing bevacizumab with best supportive care or the investigator's choice of treatment following the failure of radiotherapy, temozolomide and lomustine are lacking. To the best of our knowledge, there are also no retrospective studies on bevacizumab focusing on patients with primary glioblastoma following the failure of radiotherapy, temozolomide and lomustine. Therefore, in the present study, a database was screened for patients with primary glioblastoma who had been treated with bevacizumab for recurrent glioblastoma. The key inclusion criterion was previous treatment with radiotherapy, temozolomide and lomustine. The response rate, PFS and OS rate and time, and the influence of response on PFS and OS rate and time were evaluated.

Patients and methods

Patient selection. The database of the University Hospital Frankfurt (Frankfurt, Germany) was screened for patients with recurrent glioblastoma who were treated with bevacizumab between January 2009 and December 2016. Only patients with primary glioblastoma were included. Patients with an isocitrate dehydrogenase (IDH) 1 mutation or a previous diagnosis of a lower grade glioma were excluded. Only patients treated with radiotherapy, temozolomide and lomustine prior to the initiation of bevacizumab treatment were included, and there were no exclusion criteria. The general patient characteristics, Karnofsky performance score (KPS) at the start of bevacizumab treatment, MGMT promoter methylation status, prior treatments, number of prior recurrences and details of bevacizumab treatment were recorded. In order to evaluate response rate, magnetic resonance imaging (MRI) scans from prior to and during bevacizumab treatment were assessed, according to the Response Assessment in Neuro-Oncology (RANO) criteria (22). To estimate progression-free survival (PFS) and overall survival (OS) times, the interval from the initiation of bevacizumab treatment to the time of progression according to RANO criteria, and to the date of patient mortality from any cause, were recorded, respectively.

A number of patients from the cohort were included in previously published studies on the use of bevacizumab in recurrent glioblastoma (23-25).

Ethics and approval. The present study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All patient data were anonymized prior to statistical analysis. Ethics board approval (Ethics Committee, University Hospital, Frankfurt, Germany) was obtained for this retrospective study. No additional data was created or used aside from the retrospective evaluation of the database.

Statistical analysis. Survival analysis was performed using the Kaplan-Meier method and the log-rank test to compare the group of non-responders with the group of responders using SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics. The recorded patient characteristics are included in Table I. The median age of the patient cohort was 53 years; approximately one-third (21/62) of the patients were female. All patients had previously been diagnosed with primary glioblastoma. A total of 54.8% of the patients exhibited an unmethylated MGMT promoter and 27.4% exhibited a methylated MGMT promoter; for the remaining 17.8%, promoter methylation status was inconclusive or unknown. A total of 8.1% of the patients underwent biopsy only as the means of initial diagnosis, with no further surgical procedures, whereas 40.3% underwent ≥2 resections prior to the start of bevacizumab treatment. All patients received prior radiotherapy and 45.2% had undergone at least a second course of radiotherapy prior to treatment with bevacizumab. The median number of previous chemotherapies was 2, and according to the inclusion criteria, all patients had received prior temozolomide and lomustine chemotherapy. The median number of prior recurrences was 3.

Concomitant treatment and response rate. The majority of patients (59.7%) were treated with bevacizumab monotherapy, whereas 27.4% received irinotecan or lomustine in combination with bevacizumab (Table II). The response to therapy was evaluated according to RANO criteria by two experienced neuroradiologists and results are included in Table II. A total of 35.5% of the patients exhibited progressive disease at the first MRI follow-up scan, whereas 9.7% exhibited stable disease. These groups were regarded as non-responders. On the other hand, 51.6% of patients achieved partial remission and 3.2% achieved complete remission. These groups were regarded as responders; therefore, the response rate was 54.8%.

Table I. Patient characteristics and pretreatments (n=62).

Characteristics	Value
General	
Median age (range), years	53 (28-75)
Female, % (n)	33.9 (21)
Karnofsky performance score	
Median (range), %	80 (50-100)
50-60%, % (n)	27.4 (17)
70-80%, % (n)	45.2 (28)
90-100%, % (n)	27.4 (17)
Neuropathology, % (n)	
Primary glioblastoma	100.0 (62)
Glioblastoma with oligodendroglial component	3.2 (2)
O-6-methylguanine-DNA methyltransferase promoter status, % (n)	
Unmethylated	54.8 (34)
Methylated	27.4 (17)
Inconclusive	11.3 (7)
Unknown	6.5 (4)
Prior surgery, % (n)	
Biopsy only	8.1 (5)
One resection	51.6 (32)
Two resections	27.4 (17)
More than two resections	12.9 (8)
Prior radiotherapy, % (n)	
Prior radiotherapy	100.0 (62)
One radiotherapy	54.8 (34)
Two radiotherapies	41.9 (26)
More than two radiotherapies	3.2 (2)
Prior chemotherapy	
Median number of chemotherapies (range)	2 (2-6)
Two chemotherapies, % (n)	58.1 (36)
Three chemotherapies, % (n)	35.5 (22)
Prior temozolomide treatment, % (n)	100.0 (62)
Prior lomustine treatment, % (n)	100.0 (62)
Prior recurrences	
Median number of recurrences (range)	3 (2-5)
Two recurrences, % (n)	37.1 (23)
Three recurrences, % (n)	38.7 (24)
Four recurrences, % (n)	16.1 (10)

Table II. Concomitant treatment and response (n=62).

Characteristic	% (n)
Concomitant therapy	
Bevacizumab monotherapy	59.7 (37)
Irinotecan	16.1 (10)
Lomustin	11.3 (7)
Radiotherapy	6.5 (4)
Other	6.5 (4)
Response[a]	
Progressive disease	35.5 (22)
Stable disease	9.7 (6)
Partial remission	51.6 (32)
Complete remission	3.2 (2)

[a]According to the Response Assessment in Neuro-Oncology criteria.

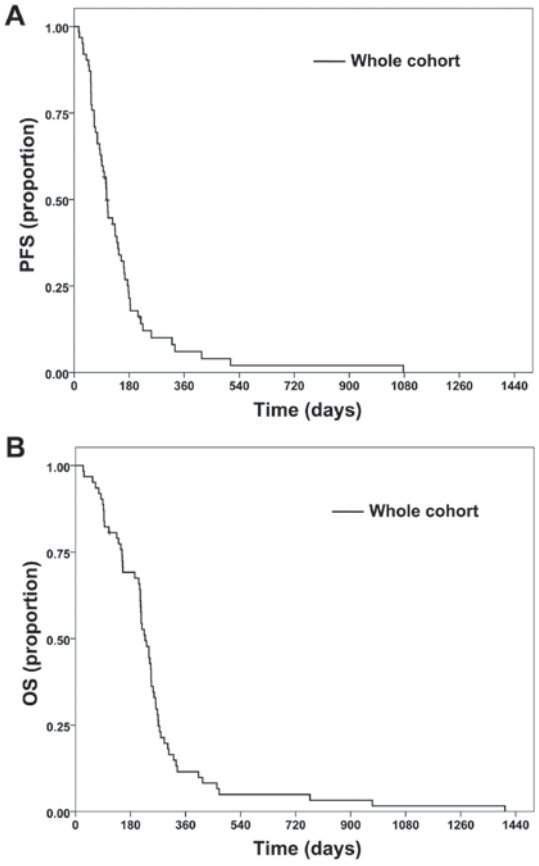

Figure 1. PFS and OS rate of the whole cohort. (A) PFS and (B) OS rate of the whole cohort. Tick marks indicate censored patients. Median PFS time was 3.5 months and PFS rate at 6 months was 21.5%. Median OS time was 7.5 months and OS rate at 12 months was 11.5%. PFS, progression-free survival; OS, overall survival.

Survival. PFS and OS times for the cohort are shown in Fig. 1. The median PFS time was 3.5 months (Fig. 1A) and the median OS time was 7.5 months (Fig. 1B). PFS rate at 6 months was 21.5%, while OS rate at 12 months was 11.5%. The median PFS time was 5.4 months for responders (Fig. 2A) compared with 1.9 months in non-responding patients (Fig. 2B; P<0.0001). The PFS rate at 6 months was also superior in responders (34.9%) compared to non-responders (7.1%; P<0.0001). The median OS time in responders was 8.6 months, whereas non-responders only reached a median of 6.4 months (P<0.0001). OS rate at 12 months was 21.3% for responders and 0% for non-responders (P<0.0001).

MGMT promoter methylation status and patient age had no significant association with OS time and rate (data not shown). By contrast, patients with a KPS of 50 or 60% exhibited

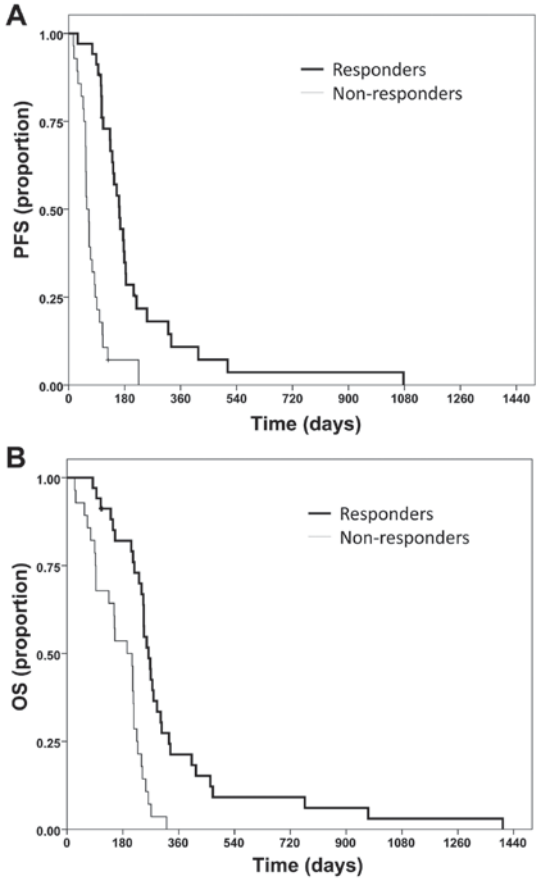

Figure 2. PFS and OS rate of responders and non-responders. Responders were defined as those with partial or complete remission; non-responders were defined as those with stable or progressive disease. Tick marks indicate censored patients. (A) PFS rate of responders (bold line) and non-responders (thin line). Median PFS time was 5.3 months for responders and 1.9 months for non-responders (P<0.0001). PFS rate at 6 months was 34.9% (responders) and 7.1% (non-responders). (B) OS rate of responders (bold line) and non-responders (thin line). Median OS time was 8.6 months for responders and 6.4 months for non-responders (P<0.0001). OS rate at 12 months was 21.3% (responders) and 0% (non-responders). PFS, progression-free survival; OS, overall survival.

a decreased median OS time (4.4 months) compared with patients with a score of 70 or 80% (8.0 months) and patients with a score of 90 or 100% (8.2 months) (data not shown).

Discussion

Bevacizumab has failed to prolong OS time when combined with radiotherapy and temozolomide chemotherapy as a first-line treatment, and at first recurrence when combined with lomustine (18-21,26). Randomized clinical trials at second or further recurrences following the failure of radiotherapy, temozolomide and lomustine are lacking. To the best of our knowledge, the present study provides the first retrospective data for patients with primary glioblastoma treated with bevacizumab following the failure of radiotherapy, temozolomide and lomustine. In contrast to previous retrospective studies, patients with lower grade gliomas or secondary glioblastoma were not included. Moreover, previous retrospective and prospective studies have included patients at the first, second or further recurrence, with patients at the first recurrence usually being the largest group of patients (16,27-34). The present study only evaluated patients who had received radiotherapy, temozolomide and lomustine prior to bevacizumab treatment. The majority of patients had undergone first-line treatment according to the Stupp protocol (1) and had received lomustine at the first progression prior to treatment with bevacizumab at the second progression. Consequently, the median number of prior chemotherapies in the cohort was 2. Patients with >2 chemotherapies usually received another course of temozolomide. In addition, >40% of the patients received a second radiotherapy; the median number of recurrences prior to bevacizumab treatment was 3. In summary, bevacizumab usually was the last line of therapy for the patients in the cohort of the present study.

Overall, >50% of patients in the cohort responded to bevacizumab treatment, with 51.6% (n=32) exhibiting partial remission and 3.2% (n=2) complete remission, according to RANO criteria. These values match or exceed the response rates from trials that predominantly enrolled patients at first recurrence (16,21,22,27-34). In line with several previous studies, this suggests that response rates do not decrease when bevacizumab is used at later progression (16,21,22,27-34).

The median PFS time of 3.5 months that was identified in the present study is in the range of previous study results. In the 'BRAIN' trial, median PFS time was 4.2 months for bevacizumab monotherapy and 5.6 months for the combination with irinotecan (16). The BELOREC trial demonstrated a median PFS time of 1.54 months for lomustine and 4.17 months for lomustine plus bevacizumab (21). Other trials, which featured a lomustine monotherapy arm at the first recurrence, exhibited a median PFS time of 1.6 and 2.7 months (35,36). Together with a PFS rate at 6 months of 21.5%, this suggests that bevacizumab is associated with a favorable PFS outcome in patients even subsequent to the failure of radiotherapy, temozolomide and lomustine.

Median OS time in the present study was 7.5 months. In the BELOREC trial, a time of 9.1 months was reported following treatment at first recurrence for the lomustine plus bevacizumab arm, and 8.6 months for the lomustine arm (21). Other trials reported a median OS of 8-9 months for patients treated at the first recurrence (16,20). Bearing in mind that the patients of the present study were treated with bevacizumab at a median of the third recurrence and that bevacizumab was typically the last-line therapy, this suggests that bevacizumab positively influenced the OS outcome.

Response rates for bevacizumab treatment have been challenged since response may only reflect the influence of bevacizumab on the contrast enhancement and edema without actually affecting tumor growth (37). Therefore, the present study also evaluated how the response to bevacizumab was associated with PFS and OS time. Responders exhibited a median PFS time of 5.4 months compared with 1.9 months in non-responders. The median OS time in responders was 8.6 months, whereas non-responders reached 6.4 months. OS rate at 12 months was 21.3% for responders and 0% for non-responders. This association between response and PFS and OS rates and times suggests that radiological response may be a surrogate marker for survival.

One explanation for this association is that bevacizumab exhibits antitumor activity. This would fit with our clinical

impression that certain patients benefit from treatment with bevacizumab. A detailed gene expression analysis of the cohort from the AVAGlio study corroborates this impression; patients with an IDH1 wild-type proneural glioblastoma exhibited an increase in OS of 4.3 months (38). Our previous studies in a relevant number of patients with glioblastoma identified radiological biomarkers suggesting that bevacizumab may exhibit antitumor activity (23,24). In the first of these studies, ~60% of bevacizumab treated patients developed tumor calcifications; survival statistics were superior for these patients (23). In the second study, 28% of the patients treated with bevacizumab developed MRI lesions that were T1 hyperintense and exhibited restricted diffusion. These patients exhibited superior median OS times (13 vs. 6.6 months) and histological analysis of these lesions revealed extensive calcified necrosis with no viable tumor cells (24). Alternately, the influence of bevacizumab on OS time could be conferred by the reduction of edema or the incidental treatment of radiation necrosis. The latter may be unlikely in the present study, as patients were significantly pre-treated, and the time from initial radiotherapy was, in general, >6 months.

The combination of bevacizumab with re-irradiation is another promising concept for the therapy of glioblastoma. This may not only reduce the risk of pseudoprogression, but also enhance the efficacy of re-irradiation due to the initially improved perfusion and oxygenation of the tumor. Prospective, randomized and controlled trials to consider this combination are missing. Schnell *et al* (39) recently reported on promising results for this combination in a large retrospective cohort: Patients that received re-irradiation and bevacizumab showed a median OS of 13.1 months. The results were further corroborated by a retrospective Italian study (40). Median OS was 11 months for patient that received re-irradiation with bevacizumab and 8.3 months for patients that received re-irradiation with fotemustin.

Due to the retrospective design of the present study and the limited number of patients, the results should be interpreted cautiously. A comprehensive evaluation of quality of life and neurocognitive function in the patient cohort was not considered; this is of particular importance, since the clinical situation of numerous patients can improve due to resolving edema and mass effect, and reducing steroid intake. It is also unclear whether bevacizumab may have adverse effects on neurocognitive function (18,41). The more general side effects of bevacizumab are of comparably minor relevance in these heavily pretreated patients without further treatment options.

None of the patients of the cohort from the present study were suitable for another resection or further radiotherapy; 45.2% had already undergone radiotherapy twice. In the EU, temozolomide and nitrosourea (lomustine) are the only drugs approved for the treatment of glioblastoma. Besides bevacizumab, no other therapeutic option was available for the patients. Thus, the response rate and the PFS and OS times and rates are promising for this heavily pre-treated cohort receiving bevacizumab as last-line therapy subsequent to the failure of all approved options. Together with the association of response with superior survival time and rate, the results indicate that bevacizumab may exhibit activity in glioblastoma as a last-line treatment. It is proposed that these results justify the reimbursement of bevacizumab in these heavily pretreated patients.

Considering the negative results from first-line trials and trials at first recurrence together with the results of the present retrospective study, a randomized trial comparing bevacizumab with precisely defined best supportive care (42,43), or investigator's choice of therapy, is advised.

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